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Evaluation of Guideline-Recommended Combined Antiretroviral Treatment Regimens in Commercially-Insured Patients Living in the United States Between 2007 and 2009

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Evaluation of Guideline-Recommended Combined Antiretroviral Treatment Regimens in
Commercially-insured patients living in the United States between 2007 and 2009

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the
requirements for the degree of
Master of Public Health
in the
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By
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ABSTRACT

Background: Randomized clinical trials of combination antiretroviral therapy (cART) inform the use of specific antiretrovirals (ARV) and their combination for optimizing therapeutic efficacy. It is critical that patients have access to and receive the most appropriate first-line treatment.

Objective: To examine factors that impact receiving initial guideline-recommended cART within a cohort of commercially insured patients in the United States (US)

Research Design: A population based cohort study.

Data Sources: A secondary administrative insurance claims database.

Subjects: Employed, commercially insured individuals with HIV who were continuously eligible for insurance coverage from January 2007 through December 2009 and received a new ARV prescription.

Measures: The primary outcome was defined as an initial claim for a prescription containing recommended cART consisting of two nucleoside reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor, protease inhibitor or an integrase strand transfer inhibitor. Modified Poisson adjusted multivariable models including patient demographic and provider characteristics evaluated predictors of receiving recommended cART.

Results: Of the 2,115 patients with a new ARV claim, 59% were white and 71% were male with a median age of 42 years (Interquartile Range: 35-49). Overall, 76% of the population received recommended cART. Receiving care from an infectious disease specialist was the strongest predictor of receiving recommended cART (Risk Ratio: 1.37, 95% Confidence Interval (CI):

1.30, 1.43). Men, those with less education, younger individuals, and no comorbidities were also more likely to receive recommended cART ($p < 0.01$).

Conclusions: Many HIV-infected patients that are in clinical care are not prescribed recommended cART. Increased communication and training of healthcare providers is necessary to insure patients receive a durable first-line regimen.

Keywords: guideline recommended cART, provider specialty

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a retrovirus that infects CD4 cells, destroying the immune system and eventually making an infected individual prone to opportunistic infections. The virus is known to spread through blood, sexual fluids, and breast milk.¹ Though the first cases of Acquired Immunodeficiency Syndrome (AIDS) were diagnosed in the 1970's, the causal relationship between the HIV and AIDS was not established until 1984.² Since its discovery, the HIV epidemic had killed 700,000 people within the United States and 39 million people around the globe.³ However, incidence began decreasing in 1996 due to the introduction of combined antiretroviral therapy which resulted in a significant reduction in HIV-related mortality rates. Public health efforts, focusing on prevention and education, have also contributed to the fact that in 2013, incidence was declining in 39 countries.⁴ Though cases in the developing world represent roughly two thirds of current HIV disease burden, industrialized nations have improved HIV care; therefore, HIV is transitioning to a chronic disease state in regions such as North America and Europe due to increased life expectancy from antiretroviral medications.⁵

The FDA has currently approved 37 antiretroviral (ARV) medications consisting of 5 general groups which each target a different part of the virus's life cycle. First, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) are the backbone of HIV therapy and target the virus's replication within the cell. Non-Nucleotide Reverse Transcriptase Inhibitors, like NRTIs inhibit the reverse transcriptase enzyme and prevent replication. However, NNRTIs do not mimic natural substrates and bind to a different active site.⁶ Protease Inhibitors, which are often boosted by addition of ritonavir, prevent the maturation of the in virus into its fully infectious form. Integrase Strand Transfer Inhibitors (ISTIs) prevent viral DNA from being integrated into host

cell DNA during the replication process. Finally, both co-receptor antagonists and fusion inhibitors prevent entry of the virus into the host cell.⁷ Due to their differing mechanisms, these medications are used in combination to reduce a patient's viral load and prevent progression of the disease as well as to reduce the transmission of the virus to others.

As the number of HIV medications has increased, prescribing of these medications has become increasingly complex due to both the number of options and the ability to individualize therapy.⁸ This can lead to inappropriate prescribing patterns. Randomized clinical trials of combination antiretroviral therapy (cART) have informed the use of specific ARVs and their combination for optimizing therapeutic efficacy. Therefore, since 1998, the United States (US) Department for Health and Human Services (DHHS) has published evidence-based guidelines for treatment of HIV-infected patients using ARVs in order to provide guidance to prescribers.⁹ Over time, these guidelines have been systematically updated, leading to significant changes in prescribing recommendations over the last 16 years. For example, in May 2006, the DHHS Panel recommended that “an initial regimen contain two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) + a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted or unboosted protease inhibitor (PI)”.¹⁰ Updates were published in December 2007 and January 2008.¹¹

Despite continuous advances in the diagnosis and treatment of individuals living with HIV, there are still an estimated 50,000 incident cases of HIV each year in the United States.¹² The DHHS guidelines make it clear that certain regimens should be avoided due to toxicity, resistance potential, drug interactions, and reduced efficacy and studies have shown improved outcomes for patients who use guideline-recommended treatment regimens.^{10,13} Furthermore, first-line ARV

treatment currently represents an estimated 39.4% of the total cost of care for an HIV-infected patient. Therefore, it is important to assess the receipt of ARV regimens that follow national guidelines in order to ensure a high quality of care for HIV-infected patients and to prevent incident cases of HIV.¹⁴

Several studies have evaluated concordance with practice guidelines both in the US and abroad through small cohorts or public insurance claims data.^{13,15-21} However, most US studies analyzed prescribing practices before 2006, and very few studies have examined private insurance data to evaluate DHHS guideline adherence. Using a private insurance claims database is advantageous as it provides a broader understanding of how guidelines are being implemented in the general population of the US. Also, a reassessment of predictive factors of appropriate care is important in order to understand the evolution and status of treatment in the HIV-infected patient population. Therefore, this study evaluates factors associated with appropriate initiation of guideline-recommended ARV treatment among HIV-infected patients with private insurance from 2007 to 2009.

METHODS

Study Design:

We constructed a cohort of HIV-infected patients using a secondary administrative claims database of employed, commercially insured individuals with dependents who were continuously eligible for insurance coverage from January 2007 through December 2009. This nationally representative database contains information such as enrollment data, inpatient/outpatient insurance claims, diagnosis codes, and claims for prescription medications that were covered by the insurance provider. Among HIV-infected patients that were incident users of ARVs, we

examined factors that predicted each patient's likelihood of receiving ARVs that are part of guideline recommended cART compared to those that received ARVs that were not part of a guideline recommended treatment regimen.

Study Population

Our study population included commercially insured patients living with HIV that were at least 18 years of age and were incident users of common first line ARVs. Patients were considered to be HIV positive if they had a claim containing an *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* diagnosis code indicative of HIV (042) or a pharmacy claim containing a National Drug Code (NDC) for an FDA approved ARV. Incident users of ARVs were defined as patients who had a claim for at least one ARV following a period of 180 days without an ARV claim. Regimens were defined as a set of ARVs that were filled on the same day and ordered sequentially. Initial regimens were defined as the initial combination of medications that a patient filled together for at least 7 days. Patients with only one regimen for less than 7 days were excluded from the analysis. Finally, since certain Nucleoside Reverse Transcriptase Inhibitors (NRTIs) can be used as monotherapy or dual therapy to treat Hepatitis B infections, patients were excluded if their records contained an ICD-9 Code for Hepatitis B (070.XX) but did not contain an ICD-9 Code for HIV or if their prescription records contained Epivir HBV and they did not have an HIV diagnosis code.

Study outcomes and measurements

Initial ARVs were categorized by the number of ARVs as well as the medication classes that comprised each regimen, according to the DHHS guidelines. Monotherapy and dual therapy

were defined as a regimen containing one or two medications, respectively. Patients taking three NRTIs simultaneously were categorized as Triple NRTI therapy. Regimens with two NRTIs as a base were categorized by the third drug in the regimen: Non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), ritonavir boosted protease inhibitor (Boosted PI), Integrase Strand Transfer Inhibitor (ISTI).

Using the DHHS guidelines from May 2006 to January 2008, we classified regimens into two categories, guideline recommended and non-guideline recommended. Monotherapy, dual therapy, and triple NRTI therapy were all considered non-guideline recommended regimens. NNRTI, PI, Boosted PI and ISTI regimens were classified as guideline recommended regimens. If a regimen contained multiple drugs from multiple classes on top of a normal NRTI base, they were categorized as guideline recommended. All other ARV combinations were considered to be non-guideline recommended. (Table 1) Finally, if a patient was taking a coformulated medication, we considered the chemical entities that were contained in the coformulation and classified the regimens accordingly.

Based on previous studies, we considered a priori a list of potential predictors of guideline recommended cART as initial therapy. These factors were assessed in the claims 180 days prior to initiating ARV treatment and included available socio-demographic variables (age, race, sex, education) as well as covariates shown to be related to a patient's overall health condition (i.e. frailty)²², including the presence of comorbidities represented by the Charlson comorbidity index²³ and overall number of healthcare claims (healthcare utilization). As we hypothesized that provider specialty and location may impact the type of regimen received, we examined whether a patient had any claims associated with an infectious disease (ID) specialist and individual's geographic location (Northeast, Southeast, Midwest, Rocky, Pacific). To examine trends in ARV

prescribing we assessed changes in the types of regimens received by calendar year. We also included year of initiation in bivariable and multivariable analyses to identify changes in ARV receipt over the study period.

The Predictive Model

The model used in this study is primarily predictive. Therefore, it takes known information about a population and predicts the incidence of an outcome based on these factors, whether or not they are causally related to the outcome. This serves a different purpose from epidemiologic models which are used to explain an outcome using known causal associations and represent a picture of elements that lead to a disease or outcome. Predictive models have many uses in setting up randomized clinical trials, establishing screening guidelines, and identifying high risk groups in order to increase efficiency in interventions with limited resources.²⁴⁻²⁷

Statistical Analysis

Unadjusted bivariate analysis using χ^2 and t-test or Mann-Whitney U test statistics, where appropriate, were performed. To examine factors that predicted the receipt of guideline-recommended initial cART regimens, we used a generalized linear model with a modified Poisson distribution, log and identity links for risk ratios (RR) and risk differences (RD) respectively, and robust variance to generate 95% confidence intervals (CI).²⁸ A backwards elimination approach was used to identify a final predictive model. A priori statistical significance level was set at $\alpha = 0.05$. In order to assess the model fit, we calculated the probabilities of receiving a preferred or non-preferred regimen based on the final model. These probabilities were then compared to the actual outcomes through logistic regression in order to

output an ROC curve and calculate a concordance (c) statistic for discriminative ability. All analyses were performed using SAS statistical software v. 9.3 (Cary, NC). This study was funded, in part, by the National Institutes of Health grant numbers K12 DA035150 and UL1TR000117 through the availability of data resources and salary support.

RESULTS

Of the 10,153 patients identified as HIV positive in the claims data, we identified 2,316 patients that had an incident medical claim for at least one ARV between January 1, 2007 and December 31, 2009. After excluding patients with only one regimen for less than 7 days (N=35), those with an HIV diagnosis code with a diagnosis code for hepatitis B (N=113) or a claim containing Epivir HBV without an HIV diagnosis code (N=53), there were 2,115 patients with incident ARV use included in the analysis. Of these, 1,613 (76%) received guideline recommended cART. Compared to patients receiving recommended cART, those that did not receive guideline recommended ARV therapy were more likely to be female, black, have at least a high school education and less likely to have a claim associated with an ID specialist in bivariable analysis. (Table 2)

In multivariable analysis, provider status, sex, education, comorbidity status, and age were statistically significant while healthcare utilization, year of service, race and geography were not statistically significantly associated with receiving guideline recommended cART. Our predictive model resulted in a c statistic of 0.74. Patients having at least one claim associated with an ID specialist was the strongest predictor of recommended cART, with these individuals having 1.37 times (95% CI 1.30,1.43) the likelihood of receiving recommended cART than patients that did not have a claim associated with an ID specialist. This corresponds to a risk

difference of 0.27 (95% CI: 0.23,0.30). Therefore, for every 3.7 patients who have a claim associated with an ID specialist, 1 patient received a guideline recommended regimen who otherwise would have received a non-guideline recommended regimen. Males were also more likely to receive guideline recommended cART than women [RR: 1.24 (95% CI: 1.15,1.33)]. Patients who had more than a high school education, older patients as well as those with a Charlson comorbidity index ≥ 1 were less likely to receive recommended cART. (Table 3)

Prescribing trends were mostly consistent from 2007 to 2009 with the exception of prescription of boosted PIs and monotherapies. Monotherapies increased from 6.6% of all initial antiretroviral regimens in 2007 to 16.4% in 2009. Conversely, boosted PIs declined from 26.9% of regimens in 2007 to 16.2% of regimens in 2009. Finally, in multivariable analysis, year of initiation was not associated with guideline recommended treatment.

DISCUSSION

We found that among commercially insured HIV-infected patients initiating ARV therapy between 2007 and 2009, 24% did not receive guideline recommended treatment. Furthermore, gender, education, comorbidities, and involvement of an ID specialist were all associated with the receipt of guideline-recommended cART regimens. Indeed, this is not the first study of guideline adherence to cART. Previous researchers have demonstrated the considerable variability in adoption of HIV prescribing guidelines both in the US and other countries. In Brazil, for example, a study found that only 2% of patients were receiving inappropriate regimens according to national guidelines, but a much larger percent were using suboptimal regimens.²⁰ In the US, guideline adherence has been inconsistent. Mann et al. noted a lack of

physician adherence to guidelines involving the patient counseling and initial prescription of ARV therapy in 2000.¹⁹ Conversely, Hirschhorn et al. found that 78% of women and 82% of men in Ryan-White funded facilities were receiving recommended Highly Active Antiretroviral Therapy (HAART) between 1999 and 2001.²⁹ Fleishman et al. noted an increase in the receipt of broadly defined ARV therapy from 60% of eligible patients within the HIV Research Network in 2002 to 81% in 2008.³⁰ Notably, most of these studies were completed in patients with public insurance or at the institutional level, with the majority completed before 2006. This study provides an important contribution to the current evidence as it evaluates the initial cART receipt in commercially insured patients which allows for the understanding of broader trends in HIV medication use for patients who are not seen public hospitals or large academic research centers.

Our results demonstrate sex disparities in the receipt of guideline recommended initial cART in commercially insured patients. These results are contiguous with earlier studies which have indicated that sex was an important indicator in determining whether or not a patient would receive appropriate treatment.^{13,15,16,31-33} Results from two cross-sectional studies of the HIV Research Network spanning from 2001 to 2008 found that females were consistently less likely to receive HAART than males patients.^{30,32} In a prospective cohort study of women enrolled in the Women's Interagency Health Study between 1998 and 2004, only 53% of participants were taking a guideline-consistent regimen and these women also had poorer immunologic and virologic outcomes than those who did receive guideline recommended treatment.¹³

Many studies have documented the low rate of guideline recommended treatment in the African American Population.^{13,30,32} However, some studies at public institutions have found an inverse or null association. A study in US Veterans found that being black was significantly associated

with receiving appropriate regimens.¹⁶ In 1999, a study of Ryan White-funded Facilities found no difference in prescribing trends between age, race, or sex.¹⁷ This research also demonstrates that commercially insured black patients were equally as likely to receive care from 2007 to 2009 as their white counterparts.

We found that patients with at least a high school education were less likely to receive guideline recommended treatment. This finding is not supported by the current literature which suggests that patients of lower socioeconomic status, often measured by a low level of education, have poorer HIV outcomes.^{34,35} Our findings may be a reflection of the data source and selection, as all patients included in the study qualify for commercial insurance through an employer or through a spouse that is employed. Therefore, patients of very low-socioeconomic status are likely not represented in this data source and the relationship between education and receipt of guideline recommended treatment that we observed reveals a different aspect of health services access in the US.

Patients with a Charlson comorbidity index score of ≥ 1 were less likely to receive guideline recommended treatment. This is in accordance with observations from studies of patients with HIV and other conditions and may be a reflection of the challenge in coordinating medical care, prescribing based on drug-drug interactions or patient preference.³⁶⁻³⁹

Finally, as HIV patients are increasingly treated by providers that are not necessarily infectious disease experts, our results support a need for increased communication and dissemination of up to date information regarding HIV treatment guidelines to all health care providers. Historically, physician specialization effects have been studied through direct physician surveys. In 2001, Stone et al. surveyed 2478 internal medicine and ID physicians, with two theoretical patient

cases and found that specialty was significantly correlated with guideline recommended therapy.⁴⁰ In 2003, a survey of physicians found that self-described ID specialists and expert-generalists were more likely to comply with prescribing guidelines than non-expert generalists.⁴¹ A 2011 Cochrane review of 4 US studies concluded that patients who saw ID specialists or physicians who saw a larger number of HIV patients were more likely to receive HAART. They also noted a trend for improved clinical outcomes among HIV patients who saw ID specialists compared to patients who did not see ID specialists.⁴² In our analysis, patients who saw ID specialists were more likely to receive guideline recommended initial cART regimens. However, it is important to note that our analysis reflects whether or not a patient fills a prescription for appropriate cART regimens through insurance and does not contain any information about prescriptions that were left unfilled. It is possible that patients who seek care from ID specialists are more involved in their own care. Another explanation could be a difference in counseling on cART regimens after office visits. Furthermore, this analysis does not account for the physician's HIV patient load nor measures physician knowledge, both which have been shown to be associated with guideline-recommended treatment.

Limitations of this study are due to the nature of working with an administrative data set. No clinical data such as CD4 count or HIV viral load were included in this analysis to demonstrate appropriateness of therapy. Also, since this data contained only claims for prescriptions filled through insurance, no out-of-pocket drug expenses were accounted for. Nevertheless, the expensive nature of antiretroviral medications, it may be assumed that the number of missing "out-of-pocket" ARV medications is small. Furthermore, this analysis does not examine mortality or other health outcomes for commercially-insured patients taking guidelines-recommended or non-guideline-recommended regimens. However, since the DHHS guidelines

are written using primary literature to support improved outcomes for patients, this may be inferred.

CONCLUSION

This study demonstrates continued disparities in receipt of ARV treatment in commercially insured patients between 2007 and 2009. It also emphasized the need for dissemination of information to all health care providers regarding HIV treatment. Future studies might be designed to elucidate the underlying causes for the difference in guideline adherence due to provider type. Studies linking commercial insurance data to medical records would be helpful in determining treatment patterns and outcomes in HIV patients. Continued monitoring and evaluation of health care delivery and treatment patterns is essential in order to reduce HIV associated morbidity and mortality within the general US population.

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Table 1 : Regimen Categories		
Non-guideline recommended	Monotherapy Dual Therapy Triple NRTI* Other	1 antiretroviral medication 2 antiretroviral medications 3 NRTIs* Multiple antiretroviral classes without 2 NRTI* base
Guideline recommended	NNRTI† ISTI‡ PI§ Boosted PI§ Preferred Other	2 NRTIs* + 1 NNRTI† 2 NRTIs* + 1 ISTI‡ 2 NRTIs† + 1 PI§ 2 NRTIs† + 1 Boosted PI§ 2 NRTIs† + Multiple antiretroviral medications

*Nucleoside reverse transcriptase inhibitor

†Non-nucleoside reverse transcriptase inhibitor

‡Integrase strand transfer inhibitor

§Protease inhibitor

Table 2: Characteristics of patients overall and according to type of initial antiretroviral regimen				
	All antiretroviral initiators (n=2115) n (%)	Guideline- Recommended Treatment (n=1613) n (%)	Non-Guideline Recommended Treatment (n=502) n (%)	P-value
Patient Sex				<0.0001
Male	1835 (87)	1361 (84)	354 (71)	
Female	475 (22)	252 (16)	148 (24)	
Patient Race				<0.0001
White	1243 (59)	990 (61)	253 (50)	
Black	331 (16)	258 (16)	73 (15)	
Hispanic	269 (13)	230 (14)	39 (8)	
Other	272 (13)	135 (8)	137 (27)	
Age (median, IQR)	42 (35,49)	41 (35,48)	43 (35,52)	0.003*
Education				0.0017
< High School	821 (39)	656 (41)	165 (33)	
≥ High School	1294 (61)	957 (59)	337 (67)	
US Region				0.0002
Northeast	314 (15)	228 (14)	86 (17)	
South	1204 (57)	938 (58)	266 (53)	
Midwest	313 (15)	248 (15)	65 (13)	
Rocky	97 (5)	79 (5)	18 (4)	
Pacific	186 (9)	119 (7)	67 (13)	
ID Specialist				<0.0001
Yes	1072 (51)	942 (58)	130 (26)	
No	1043 (49)	671 (42)	372 (74)	
Charlson Comorbidity Score				<0.0001
0	1619 (77)	1317 (82)	302 (60)	
≥1	496 (23)	296 (18)	200 (40)	
Year of cART initiation				0.0082
2007	409 (19)	320 (20)	89 (18)	
2008	907 (43)	713 (44)	194 (39)	
2009	799 (38)	580 (36)	219 (44)	
Healthcare Utilization [†] (median, IQR)	14 (7, 25)	14 (7,18)	15 (7, 30)	0.0154*

*P-value determined by Mann-Whitney U test

[†]Number of healthcare claims in the 180 days prior to first antiretroviral regimen

Table 3. Risk Ratios and Risk Differences associated with receiving guideline recommended regimens		
Characteristic	Risk Ratio (95% CI*)	Risk Difference (95% CI*)
Sex		
Male	1.24 (1.15, 1.33)	0.19 (0.14, 0.24)
Female	Ref	Ref
Age (per 10 years)	0.97 (0.95, 0.99)	-0.03 (-0.04,- 0.01)
Education		
More than high School	0.91 (0.87, 0.96)	-0.08 (-0.12, -0.04)
High School or less	Ref	Ref
Infectious Disease Specialist		
Yes	1.37 (1.30, 1.43)	0.26 (0.23, 0.30)
No	Ref	Ref
Charlson Comorbidity Index		
Score of 0	Ref	Ref
Score ≥ 1	0.75 (0.70,0.81)	-0.24 (-0.29, -0.20)
*CI: Confidence Interval		

Figure 1 Legend:

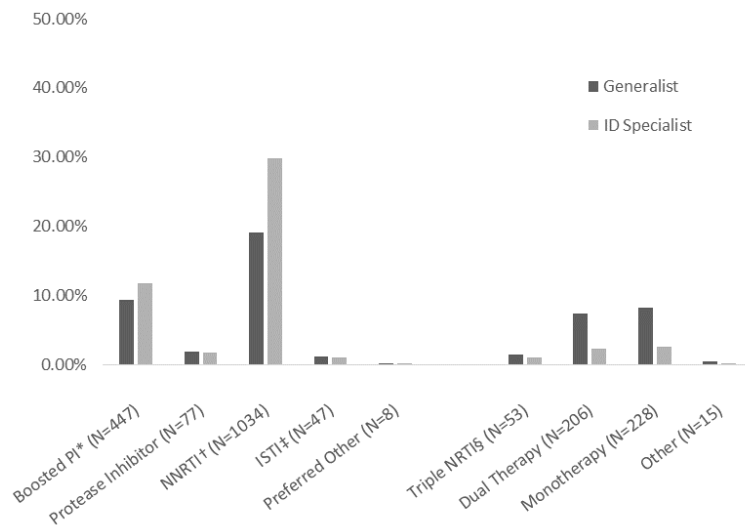
Frequency of antiretroviral regimens stratified by whether patient had interaction with an infectious disease specialist or other type of physician (generalist).

*PI: Protease inhibitor

†NNRTI: Non-nucleoside reverse transcriptase inhibitor

‡ISTI: Integrase strand transfer inhibitor

§NRTI: Nucleoside/tide reverse transcriptase inhibitor



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BIOGRAPHICAL SKETCH

Joye Brigitte Allen grew up in Trenton, MI and attended Alma College where she obtained her B.S. in French and Chemistry. Before pursuing graduate school, she worked in a Plant Biochemistry Lab at Michigan State University and served for 2 years in the US Peace Corps in Mali, West Africa with her husband. There, she completed projects such as a biweekly radio show in native Bambara, malaria prevention activities, and classroom construction. After being evacuated from Mali due to a coup d'état in 2012, Joye began attending the University of Kentucky's College of Pharmacy where she pursued a dual PharmD/MPH and will graduate in 2016. After graduation, Joye will pursue a residency at the Veterans Affairs Healthcare System in Ann Arbor, Michigan. She hopes to continue to use her epidemiology training throughout her career.